General

Guideline Title

The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of adult acute lymphoblastic leukemia: update of the 2006 evidence-based review.

Bibliographic Source(s)

ASBMT position statement. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of adult acute lymphoblastic leukemia: update of the 2006 evidence-based review. Biol Blood Marrow Transplant. 2012 Jan;18(1):16-7. [2 references] PubMed

Oliansky DM, Larson RA, Weisdorf D, Dillon H, Ratko TA, Wall D, McCarthy PL Jr, Hahn T. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of adult acute lymphoblastic leukemia: update of the 2006 evidence-based review. Biol Blood Marrow Transplant. 2012 Jan;18(1):18-36.e6. [68 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version:

ASBMT Executive Committee. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of acute lymphoblastic leukemia in adults. Biol Blood Marrow Transplant 2006 Mar;12(3):368-9. [3 references]

Hahn T, Wall D, Camitta B, Davies S, Dillon H, Gaynon P, Larson RA, Parsons S, Seidenfeld J, Weisdorf D, McCarthy PL Jr. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute lymphoblastic leukemia in adults: an evidence-based review. Biol Blood Marrow Transplant 2006 Jan;12(1):1-30. [83 references]

Recommendations

Major Recommendations

The levels of evidence (1++ to 4) and the grades of recommendations (A-D) are defined at the end of the "Major Recommendations" field.

The following updated treatment recommendations are offered for the role of stem cell transplantation (SCT) as treatment for adult lymphoblastic leukemia (ALL) in adults, and are based on consensus reached by an expert panel following a systematic review of the literature published since the 2006 original evidence-based review.

Autologous SCT versus Non-transplantation Therapy for ALL in First Complete Remission (CR1)

- New evidence indicates that in the absence of a suitable allogeneic donor, autologous SCT may be an appropriate therapy because of similar survival outcomes and a shorter treatment duration when compared with chemotherapy alone, but results in a high relapse rate. Maintenance therapy, biologic therapy, or tyrosine kinase inhibitors may improve outcomes in selected patients, but these approaches need further study. (Grade of Recommendation A, Highest Level of Evidence 1++)

Allogeneic SCT versus Non-transplantation Therapy for ALL in CR1

- New data indicate that myeloablative allogeneic SCT is an appropriate treatment for adult ALL in CR1 for all disease risk groups. Allogeneic SCT provides a significant improvement in overall and leukemia-free survival in younger (<35 years), standard risk, Ph-negative ALL patients compared with less intensive chemotherapy regimens. In older (>35 years), standard risk, Ph-negative ALL patients, a higher transplant-related mortality diminishes the significant survival advantage with allogeneic SCT. (Grade of Recommendation A, Highest Level of Evidence 1++)

Allogeneic SCT versus Non-transplantation for ALL in ≥CR2

- New data confirm the original treatment recommendation favoring allogeneic SCT over chemotherapy for ALL in CR2 or greater. (Grade of Recommendation B, Highest Level of Evidence 2++)

Autologous versus Allogeneic SCT

- New data strengthen the original treatment recommendation favoring allogeneic over autologous SCT. There are insufficient data to determine if this effect is more apparent in disease risk subgroups, including Ph+ ALL. (Grade of Recommendation B, Highest Level of Evidence 2++)

Related versus Unrelated Donor Allogeneic SCT

- New data confirm the original recommendation that there are similar, and possibly equivalent, survival outcomes after related and unrelated allogeneic SCT. Post-SCT complications may differ. (Grade of Recommendation B, Highest Level of Evidence 2++)

Unrelated Donor Cord Blood Transplant versus Unrelated Donor Bone Marrow Transplantation (BMT)

- New data indicate it is appropriate to consider cord blood transplantation for patients with no HLA well-matched donor option or those needing an urgent transplant. (Grade of Recommendation B, Highest Level of Evidence 2++)

Imatinib versus No Imatinib Pre- and/or Post-SCT in Ph-Positive ALL

- New data suggest imatinib therapy before and/or after SCT yields significantly superior outcomes in overall survival and leukemia-free survival. Ongoing studies using other tyrosine kinase inhibitors may strengthen this recommendation. (Grade of Recommendation B, Highest Level of Evidence 2++)

Comparison of Induction Therapies before SCT

- New data were insufficient to make a treatment recommendation regarding the benefit of any 1 induction regimen. (No Recommendation, Highest Level of Evidence 1++)

Allogeneic SCT: Conditioning

- There are not enough data to make a recommendation of the superiority of any 1 conditioning regimen. As in the original recommendation, there appears to be a benefit to total body irradiation-containing regimens compared with non–total body irradiation-containing regimens. (Grade of Recommendation B, Highest Level of Evidence 2++)
- New data suggest reduced-intensity conditioning may produce similar outcomes to myeloablative regimens, but are insufficient to make a recommendation on the use of reduced-intensity conditioning. Thus, reduced-intensity regimens are appropriate only for adult patients with ALL in remission who are unsuited for myeloablative conditioning. (Grade of Recommendation B, Highest Level of Evidence 2++)

Definitions:

Levels of Evidence	

Levels of Evidence	
1++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies; high-quality case control or cohort studies with a very low risk of confounding, bias, or chance, and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance, and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding, bias, or chance, and a significant risk that the relationship is not causal
3	Nonanalytic studies (e.g., case reports, case series)
4	Expert opinion

Grades of Recommendation	
A	At least one meta-analysis, systematic review, or randomized controlled trial (RCT) rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

Source: Harbour R, Miller J. A new system for grading recommendations in evidence-based guidelines. *Br Med J*. 2001;323:334-336.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Acute lymphoblastic leukemia (ALL)

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Hematology

Internal Medicine

Oncology

Pathology

Intended Users

Health Plans

Managed Care Organizations

Patients

Physicians

Guideline Objective(s)

- To assemble and critically evaluate all valid, peer-reviewed evidence regarding the role of cytotoxic therapy with hematopoietic stem cell transplantation (SCT) in the therapy of adult acute lymphoblastic leukemia (ALL)
- To provide treatment recommendations based on the available evidence
- To identify discrepancies in study design or methodology among published studies that may impact the quality of the evidence
- To identify areas of needed research

The goals of the Adult ALL Evidence-Based Review (EBR) update are:

- To provide a summary of recent clinical evidence
- To provide timely treatment recommendations
- To determine if new evidence strengthens or changes treatment recommendations provided in the original Adult ALL EBR published in 2006

Target Population

Adult patients (≥18 years) with acute lymphoblastic leukemia (ALL)

Interventions and Practices Considered

1. Myeloablative allogeneic stem cell transplantation (SCT)
2. Chemotherapy
3. Autologous SCT
4. Related donor allogeneic SCT
5. Unrelated donor allogeneic SCT
6. Cord blood SCT
7. Imatinib therapy pre- and/or post-SCT in Ph-positive acute lymphoblastic leukemia
8. Conditioning regimens

Major Outcomes Considered

- Complete remission of patients with acute lymphoblastic leukemia (ALL)
- Extended leukemia-free survival
- Disease-free, event-free, and overall survival
- Treatment-related mortality

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Methodology for the Adult Acute Lymphoblastic Leukemia (ALL) Evidence-Based Review (EBR) Update

The SCOPUS database, which includes PubMed and Medline, the Websites developed by the National Center of Biotechnology Information at the National Library of Medicine of the National Institutes of Health, were first searched on July 29, 2010, using the search terms "acute lymphoblastic leukemia" OR "ALL" AND "transplant" limited to "human trials," "English language," and a publication date of January 1, 2005 or later. An updated search was conducted on October 15, 2010. In addition to the online database searches, a manual search of the reference lists of the included articles and relevant reviews published since January 2005 was conducted.

Papers that were published before January 2005, included fewer than 25 ALL patients, or were not peer-reviewed were excluded. Also excluded were editorials, letters to the editor, Phase I (dose escalation or dose finding) studies, reviews, consensus conference papers, practice guidelines, and laboratory studies with no clinical correlates. Abstracts and presentations at national or international meetings were not used for the treatment recommendations in this update for reasons previously described. However, abstracts are included in the "Areas of Needed Research and Ongoing Studies" section for the reader's information.

Several of the studies evaluated for inclusion in this adult ALL update included patients with acute myeloid leukemia (AML); therefore, to be included, at least 65% of a study's patients had to have ALL, unless the results were stratified by disease.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence	
1++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies; high-quality case control or cohort studies with a very low risk of confounding, bias, or chance, and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance, and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding, bias, or chance, and a significant risk that the relationship is not causal
3	Nonanalytic studies (e.g., case reports, case series)

Levels of Evidence	
4	Expert opinion

Source: Harbour R, Miller J. A new system for grading recommendations in evidence-based guidelines. *Br Med J*. 2001;323:334-336.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The hierarchy of evidence, including a grading system for the quality and strength of the evidence and strength of each treatment recommendation, was published as an editorial policy statement in *Biology of Blood and Marrow Transplantation (BBMT)* in 2005 (see the "Rating Scheme for the Strength of the Evidence" and the "Rating Scheme for the Strength of the Recommendations" fields). The hierarchy defines criteria used to grade the studies that were included in this update and criteria to grade the treatment recommendations, respectively. Study design, including sample size, patient selection criteria, duration of follow-up, and treatment protocol also were considered in evaluating the studies. Clinical studies are described in the tables with sufficient detail to give a concise summary of study design and patient outcomes.

All data in the text and tables were abstracted from the original manuscripts by one author and double checked for accuracy and clarity by 2 other authors. Some articles contained inconsistencies within the data reported; the data most consistent with the text of the article were included in this review.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

In 1999, the American Society for Blood and Marrow Transplantation (ASBMT) began developing systematic evidence-based reviews (EBR) and position statements on the effectiveness of autologous and allogeneic hematopoietic stem cell transplantation (SCT) for specific diseases. In 2009, the ASBMT EBR Steering Committee determined that previously published reviews should be updated regularly at approximately five-year intervals. The same expert panel members associated with the original EBR are invited to participate in the update process as well.

Expert Panel Selection for Evidence-Based Review (EBR) Update

To achieve an appropriate balance, physicians who have extensive clinical experience and published research studies using stem cell transplantation (SCT) and other therapies in the treatment of the specific disease of interest are invited to join an independent expert panel that examines the summarized literature and provides subsequent treatment recommendations based on the available evidence. Potential panelists are restricted to U.S.-based institutions for two reasons: (1) ease of logistics in convening teleconferences, and (2) differences in the healthcare systems and health insurance coverage between the United States and other countries (including Canada, Europe, etc.), which may result in different expert recommendations based on considerations of costs and access to care. In addition to clinical and research physicians, at least one third-party payer representative, a patient advocate, and a liaison to the American Society for Blood and Marrow Transplantation (ASBMT) Steering Committee are invited to serve on the panel.

Consensus Process for Treatment Recommendations

The consensus process involves a teleconference during which panelists critically discuss the evidence for each section of the review and develop initial treatment recommendations according to the categories in the "Rating Scheme for the Strength of the Recommendations" field. The information is summarized by the primary authors in tabular form and distributed to the panelists for additional review and clarification. Any changes suggested by an individual panelist are circulated for review and approval by all panelists. This iterative process concludes when a final version of the Treatment Recommendations Table is approved by all panelists.

Rating Scheme for the Strength of the Recommendations

Grades of Recommendation	
A	At least one meta-analysis, systematic review, or randomized controlled trial (RCT) rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

Source: Harbour R, Miller J. A new system for grading recommendations in evidence-based guidelines. *Br Med J*. 2001;323:334-336.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

After the final draft of the Adult Acute Lymphoblastic Leukemia (ALL) Evidence-Based Review (EBR) Update is approved by the expert panel it is reviewed by the American Society for Blood and Marrow Transplantation (ASBMT) EBR Steering Committee and then submitted to the Biology of Blood and Marrow Transplantation (BBMT) journal for peer-review. Any changes requested during the peer-review process must be reviewed and approved by all the expert panelists.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of cytotoxic therapy with hematopoietic stem cell transplantation in adult patients with acute lymphoblastic leukemia

Potential Harms

Treatment-related toxicity and mortality

Qualifying Statements

Qualifying Statements

Limitations of the Evidence-Based Literature Review

The strengths of this updated systematic evidence-based review are the details about each study's design and outcomes conveyed in the summary tables for each major section, and the consensus treatment recommendations made by the adult acute lymphoblastic leukemia (ALL) expert panel. A limitation is the exclusion of nonpeer-reviewed data. Unpublished data can represent "negative" findings that could lead to publication bias; however, the inclusion of high-quality, peer-reviewed publicly available data was of paramount importance. With the exception of the Ongoing Studies section, data published in abstract form were not included in this review because of the inadequate details of study design or patient characteristics, making a true assessment of the widespread applicability or impact of the treatment outside the scope of the trial difficult.

The quality of this systematic evidence-based reviews (EBR) is affected by treatment modalities that vary over time. Chemotherapy regimens, human leukocyte antigen (HLA) typing techniques, novel pre- and post-stem cell transplantation (SCT) biologic and tyrosine kinase inhibitor therapies, and post-SCT supportive care change considerably over the course of these reviews and updates. The clinical research process is lengthy, making data from many of these studies outmoded by the time of publication. Much of the new data presented in this updated EBR may be obsolete in terms of the current standard of care, stressing the need for more timely updates of the EBRs. In addition, the lengthy process of conducting and reporting clinical research emphasizes the need to identify surrogate endpoints or molecular markers that are predictive of long-term survival in adult ALL patients. Further delineation of clinical risk factors may facilitate appropriate selection of ALL patients for SCT.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2006 Feb (revised 2012 Jan)

Guideline Developer(s)

American Society for Blood and Marrow Transplantation - Professional Association

Source(s) of Funding

American Society for Blood and Marrow Transplantation

Major funding for the review was provided by the National Marrow Donor Program.

Guideline Committee

Adult Acute Lymphoblastic Leukemia (ALL) Expert Panel

Composition of Group That Authored the Guideline

Expert Panel Members and Authors of the Review: Denise M. Oliansky, Roswell Park Cancer Institute (RPCI), Buffalo, NY; Richard A. Larson, University of Chicago, Chicago, IL; Daniel Weisdorf, University of Minnesota, Minneapolis, MN; Hildy Dillon, The Leukemia & Lymphoma Society, White Plains, NY; Thomas A. Ratko, Blue Cross Blue Shield Association Technology Evaluation Center, Chicago, IL; Donna Wall, University of Manitoba/Cancer-Care Manitoba, Winnipeg, Manitoba, Canada; Philip L. McCarthy Jr., RPCI, Buffalo, NY; Theresa Hahn, RPCI, Buffalo, NY

Financial Disclosures/Conflicts of Interest

The authors have no financial conflicts of interest to disclose.

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Guideline Availability

Electronic copies: A list of American Society for Blood and Marrow Transplantation (ASBMT) documents, along with links to individual position statements and evidence-based reviews are available in Portable Document Format (PDF) from the ASBMT Website .

Print copies: Available from Theresa Hahn, PhD, Roswell Park Cancer Institute, Medicine, Elm and Carlton Sts, Buffalo, NY 14263 (e-mail: theresa.hahn@roswellpark.org).

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on November 13, 2009. The information was verified by the developer on December 16, 2009. This NGC summary was updated by ECRI Institute on June 11, 2012. The updated information was verified by the guideline developer on July 12, 2012.

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